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P01/7700 0.00-0303097.0

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1. Your reference

PC25687

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11 FEB 2003 0303097.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

06892673001

Patents ADP number *(if you know it)*

United Kingdom

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

CRYSTALLINE THERAPEUTIC AGENT

5. Name of your agent *(if you have one)*

Dr. F.A. Edwards

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

UK Patent Department
Ramsgate Road,
Sandwich, Kent,
CT13 9NJ
United Kingdom

Patents ADP number *(if you know it)*

07758709001

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Claim *(s)*	6
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11. I/We request the grant of a patent on the basis of this application.

Signature: C.P. Kendall pp.

Date: 11th February 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: Dr. F.A. Edwards 01304.641687

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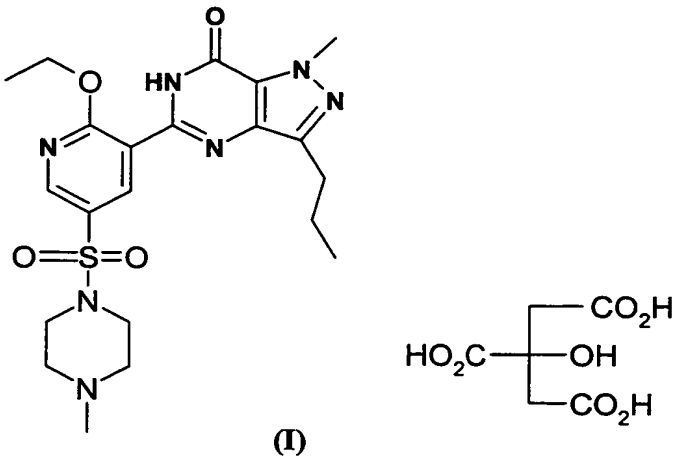
CRYSTALLINE THERAPEUTIC AGENT

The present invention relates to a novel solid form of sildenafil citrate. Anhydrous sildenafil citrate has formula (I):



(I)

In particular the present invention provides a novel hydrated form of sildenafil citrate and processes for its preparation.

Sildenafil is an orally active, potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), which is the predominant PDE5 isoenzyme in human corpora cavernosa.

Sildenafil, 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine can be prepared according to the processes disclosed in EP0463756, WO94/28902, EP0812845, and EP0994115.

Sildenafil citrate is a commercial compound marketed as Viagra ® for the treatment of male erectile dysfunction. The commercial salt is the monocitrate

salt, also known as anhydrous sildenafil citrate and has a molar ratio of sildenafil : citrate of 1 : 1.

Sildenafil monocitrate can be prepared from sildenafil free-base via acid hydrolysis techniques as are known to the skilled chemist and as exemplified hereinafter.

For successful utility within the pharmaceutical industry it is critical that the physicochemical properties of an active material are either known or can be reasonably predicted throughout the necessary processes during both its manufacture and pharmaceutical processing as well as during its shipping, storage and eventual therapeutic use. In some cases compounds can exhibit desirable medicinal properties, which cannot be translated directly into a suitable pharmaceutical composition, because the active compound itself has unsatisfactory physical properties such as for example poor chemical or processing properties.

The present invention provides a new crystalline solid form of sildenafil citrate, specifically a novel hydrated form of sildenafil citrate. The novel solid form according to the present invention has good physiochemical properties; desirable stability characteristics; desirable medicinal properties; good processing properties. The novel solid form of the present invention can be incorporated into a variety of different formulation vehicles making it especially suited for pharmaceutical utility. The stability and robustness of the hydrated solid form according to the present invention make it particularly suitable for incorporation into a variety of pharmaceutical formulations, especially aqueous based formulations.

Alternative structural forms of sildenafil citrate (polymorphs) have been proposed in "Solid Modifications in Sildenafil Citrate", Isra M. Admour, Muraz Sh. Salem, Naji Najib and A. A. Badwan (Proc. 3rd World Meeting APV/APGI, Berlin,

3/6 April 2000, pages 639 – 640). No hydrated forms of sildenafil citrate have been reported.

According to a preferred embodiment, the present invention provides a hydrated form of sildenafil citrate wherein the molar ratio of sildenafil : citrate is about 1 : 0.75.

In addition to potential formulation benefits this new, stable, crystalline material is highly desirable as crystalline materials are, in general, more stable than their amorphous counterparts, they have a finite structure which can be reproducibly characterised by powder X-ray diffraction (PXRD) which can be used to identify the presence of a specific polymorphic form.

Thus according to a further embodiment the present invention provides a novel solid form of formula (I) having a powder X-Ray diffraction (PXRD) pattern substantially as defined hereinafter.

The present invention provides a novel hydrate of sildenafil citrate. This material can be characterised by its powder X-Ray diffraction pattern (PXRD). ^{1}H Nmr can be used to characterise the relative ratios of sildenafil to citrate within the new hydrated form.

Preliminary studies indicate that the stoichiometry of this crystalline material is approximately 4 : 1 and as such this form may also be referred to as a "tetra hydrate" salt of sildenafil citrate.

Thus, according to a further aspect the present invention provides a novel solid form of sildenafil citrate, which at ambient conditions of temperature and humidity, accommodates four water molecules per unit cell. This solid form may be referred to as tetrahydrate on the basis that four water molecules are present. Analysis of this structure indicates that the water is present in the crystal lattice in

channels. Thus, the water is potentially free to move in and out of the crystal lattice dependant on the relative humidity and temperature of the environment. Such a specific hydrated material can be defined as a channel hydrate, which at ambient conditions is capable of accommodating four water molecules. Thus the hydrated solid form of sildenafil citrate according to the present invention may be defined as a tetrahydrate in terms of stoichiometry as well as a channel hydrate in terms of its 3-dimensional structure.

The preparation of the hydrated form of sildenafil citrate having the formula (I) according to the present invention may be carried out as illustrated in the Example and Preparations sections hereinafter.

The hydrated form of sildenafil citrate according to the present invention can be prepared either from sildenafil citrate or from sildenafil free-base. Starting from sildenafil citrate the hydrated form can be generated via treatment with a solution of an acidic buffer at a pH in the range of from about 4 to about 7.5.

For conversion from sildenafil citrate any acidic buffer can be used which is capable of delivering the requisite pH range. Suitable methods for the preparation of buffers for use herein are described in the Examples section hereinafter. The skilled chemist may utilise alternative methodologies as are known in the art for the preparation of acid/base buffers having the desired pH range. Suitable pH ranges for use herein include buffered solutions having a pH ideally greater than about 3.8 and less than about 8, preferably between about 4 to about 7.5, more preferably between about 5 and 7.5, yet more preferably between about 6.3 and about 7.3, and especially between about 6.4 and about 7.2. Such treatment with acid/base buffer in this pH range comprises mixing the acid/base buffer solution and sildenafil citrate together at the desired pH.

Whilst any buffer capable of delivering a pH solution in the range of from about 4 to about 7.5 may be used, preferred herein are acid/base buffers

produced from acetic, citric or phosphoric acid. Most preferred as buffering agents herein are solutions of at : pH 7.2 using 0.2M phosphoric acid with sodium hydroxide buffer ; and at pH 6.4 using 0.2M citric acid with sodium hydroxide. Especially preferred is a pH 7.2 solution using 0.2M phosphoric acid with sodium hydroxide buffer.

The reaction can be carried out at from about 0°C to about room temperature, preferably from about 25°C to about 35°C. Any suitable starting concentration of sildenafil citrate in the buffer solution can be used provided a slurry is achieved. Preferred herein are slurries, which can be stirred using regular stirring equipment such as a magnetic stirrer flea or a mechanical stirrer rod. Especially preferred herein are slurries in the range of from about 100mg/ml to about 150mg/ml and most especially about 125mg/ml slurry of sildenafil citrate in a buffered solution. The timing of the reaction will depend upon the pH of the buffer solution, the temperature of the reaction and the concentration and particle size of the sildenafil citrate. Ideal temperature ranges would be between the freezing point of the slurry (dependant on the buffer system used) and ambient temperature. Preferred for use herein are temperatures in the range of from about 4 to ambient temperature (about 25°C). Highly preferred herein is the preparation of the novel solid form of sildenafil citrate at from about 4°C to about 25°C in a buffered solution at pH from about 6.3 to about 7.3, more preferably from about 6.4 to about 7.2 and especially about pH 7.2, wherein the buffer is selected from the phosphoric and citric acid/base buffers described hereinbefore and is preferably a phosphoric acid/base buffer.

The reaction can be carried out from up to 12 hours to in excess of 72 hours, preferably from about 12 to about 36, more preferably from about 12 to about 24 hours.

The novel solid form of sildenafil citrate according to the present invention can be characterised using a variety of analytical techniques. Powder X-Ray

Diffraction (PXRD) was used to assess the structure of the solid form. Differential Scanning Calorimetry (DSC) was used to identify at which temperature ranges the solid form of the invention degraded. Thermogravimetric analysis (TGA) was used to qualify the relative weight loss when a sample of the solid form was heated from room temperature to about 80°C. Mass spectrometry was used in combination with TGA to identify any components lost during heat treatment of the solid form.

According to an alternative preparation the hydrated form of sildenafil citrate according to the present invention can be prepared by treating a mixture of sildenafil free-base and citric acid (anhydrous or monohydrate) at a range of high water activities in an organic solvent. High water activity as defined herein means 0.9 and above and is defined as the ratio of what the vapour pressure of water would be in the organic solvent / water mixture compared to pure water at that temperature. Preferred is a water activity of 0.95 and above, highly preferred is from about 0.98 to about 1.0. Suitable solvent / water mixture are reported in Zhu, H., Yuen, C., Grant, D. J. W., Int. J. Pharm. 135(1996), pages 151 to 160 the contents of which are included herein by reference. Preferred for use herein are solvent / water ratios of methanol / water in a volume (%) ratio of from at least about 10 / 90, more preferably about 5 / 95.

Preferred herein as solvent is methanol, alternative solvents such as ethanol, isopropanol, acetone or any other organic solvent can be used. Temperature range is from about -10°C to about 50°C, preferably from about 0°C to about 20°C, more preferably from about 10°C to about 15°C. The reaction can be carried out from about a few minutes to up to about 24 hours, preferably from about 12 to about 24 hours.

The reaction can be carried out with a relative excess of citric acid (to sildenafil free base). Alternatively the reaction may equally be carried out with

amounts of sildenafil free base : citric acid in the range of from about 2 : 3 to about 2 : 1, preferably from about 1 : 1 to about 2 : 1, more preferably about 4 : 3.

Further details of these methodologies are contained in the Experimental section hereinafter.

Formulations

The compound of the present invention may be use in freeze-drying, spray drying, or evaporative drying processes to provide a solid plug, powder, or film of crystalline or amorphous material. Microwave or radio frequency drying may also be used for this purpose.

The compound of the invention may be administered alone or in combination with other drugs and will generally be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound of the invention. The choice of excipient will to a large extent depend on the particular mode of administration.

ORAL ADMINISTRATION

The compound of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compound of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

The composition of a typical tablet in accordance with the invention may comprise:

Ingredient	% w/w
Sildenafil Citrate Tetrahydrate	10.00*
Microcrystalline cellulose	64.12
Lactose	21.38
Croscarmellose sodium	3.00
Magnesium stearate	1.50

* Quantity adjusted in accordance with drug activity.

A typical tablet may be prepared using standard processes known to a formulation chemist, for example, by direct compression, granulation (dry, wet, or melt), melt congealing, or extrusion. The tablet formulation may comprise one or more layers and may be coated or uncoated.

Examples of excipients suitable for oral administration include carriers, for example, cellulose, calcium carbonate, dibasic calcium phosphate, mannitol and sodium citrate, granulation binders, for example, polyvinylpyrrolidine,

hydroxypropylcellulose, hydroxypropylmethylcellulose and gelatin, disintegrants, for example, sodium starch glycolate and silicates, lubricating agents, for example, magnesium stearate and stearic acid, wetting agents, for example, sodium lauryl sulphate, preservatives, anti-oxidants, flavours and colourants.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release. Details of suitable modified release technologies such as high energy dispersions, osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). Other modified release formulations are described in US Patent No. 6,106,864.

PARENTERAL ADMINISTRATION

The compound of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of the compound of the present invention when used in the preparation of parenteral solutions may be increased by suitable processing, for example, the use of high-energy spray-dried dispersions (see WO 01/47495) and/or by the use of appropriate formulation techniques, such as the use of solubility-enhancing agents. The compound of the present invention may be present in either its crystalline or amorphous form in such formulations.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

TOPICAL ADMINISTRATION

The compound of the invention may also be administered topically to the skin or mucosa, either dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by iontophoresis, electroporation, phonophoresis, sonophoresis and needle-free or microneedle injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release. Thus compounds of the invention may be formulated in a more solid form for administration as an implanted depot providing long-term release of the active compound.

INHALED/INTRANASAL ADMINISTRATION

The compound of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as dichlorofluoromethane.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the active compound comprising, for example, ethanol (optionally, aqueous ethanol) or a suitable alternative agent for dispersing, solubilising, or extending release of the active, the propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents, which may be used instead of propylene glycol, include glycerol and polyethylene glycol.

Capsules, blisters and cartridges (made, for example, from gelatin or HPMC) for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and

a performance modifier such as *l*-leucine, mannitol, or magnesium stearate.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve that delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from about 0.05 to about 10 mg the compound of formula (I). The overall daily dose will typically be in the range 1 to 50 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

RECTAL/INTRAVAGINAL ADMINISTRATION

The compound of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate. Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted and programmed release.

OCULAR/ANDIAL ADMINISTRATION

The compound of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and andial administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic

acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/andial administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled dual-, targeted, or programmed release.

ENABLING TECHNOLOGIES

The compound of the invention may be combined with soluble macromolecular entities such as cyclodextrin or polyethylene glycol-containing polymers to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

DOSAGE

For oral and parenteral administration to human patients, the daily dosage level of the compounds or salts or solvates thereof will usually be from 10 to 500 mg (in single or divided doses).

Thus, for example, tablets or capsules of the compounds or salts or solvates thereof may contain from 5mg to 250 mg of active compound for administration

singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will also appreciate that, in the treatment of certain conditions (including MED and FSD), compounds may be taken as a single dose on an "as required" basis (i.e. as needed or desired).

These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

Generally, in humans, oral administration is the preferred route, being the most convenient and, for example in MED, avoiding the well-known disadvantages associated with intracavernosal (i.c.) administration. A preferred oral dosing regimen in MED for a typical man is from 25 to 250 mg of compound when required. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, sublingually or buccally.

Thus the invention provides a pharmaceutical composition comprising the novel solid hydrated form of sildenafil citrate according to the present invention together with a pharmaceutically acceptable diluent or carrier.

It further provides a veterinary formulation comprising the novel hydrated solid form of sildenafil citrate according to the present invention together with a veterinarily acceptable diluent or carrier.

Medical Use

The compound of the invention is useful because it possesses pharmacological activity in animals, especially mammals, including humans.

According to a further aspect of the invention there is provided the compounds of the invention for use as pharmaceuticals, and for use as animal medicaments.

Thus the invention provides a pharmaceutical composition comprising the novel solid hydrated form of sildenafil citrate according to the present invention together with a pharmaceutically acceptable diluent or carrier.

The present invention further provides a veterinary formulation comprising the novel hydrated solid form of sildenafil citrate according to the present invention together with a veterinarily acceptable diluent or carrier.

According to a yet further aspect of the invention there is provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a medical condition in which a cGMP PDE (e.g. cGMP PDE5) is indicated. There is further provided the use of the compounds of the invention in the manufacture of a medicament for the treatment of a medical condition in which inhibition of a cGMP PDE (e.g. cGMP PDE5) is desirable.

By the term "treatment", we include therapeutic (curative), palliative or prophylactic treatment.

The compound of the invention is thus expected to be useful for the curative, palliative or prophylactic treatment of mammalian sexual disorders. In particular, the compounds are of value in the treatment of mammalian sexual dysfunctions such as male erectile dysfunction (MED), impotence, female sexual dysfunction (FSD), clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder or female sexual orgasmic

dysfunction (FSOD) as well as sexual dysfunction due to spinal cord injury or selective serotonin re-uptake inhibitor (SSRI) induced sexual dysfunction but, clearly, will be useful also for treating other medical conditions for which a potent and selective cGMP PDE5 inhibitor is indicated. Such conditions include premature labour, dysmenorrhoea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, e.g. post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, diseases and conditions of the eye such as glaucoma, optic neuropathy, macular degeneration, elevated intra-occular pressure, retinal or arterial occulsion and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome (IBS).

Further medical conditions for which a potent and selective cGMP PDE5 inhibitor is indicated, and for which treatment with the compound of the present invention may be useful, include pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic nephropathy, neuropathy including autonomic and peripheral neuropathy and in particular diabetic neuropathy and symptoms thereof (e.g. gastroparesis), peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure, haemorrhoids, hypoxic vasoconstriction, diabetes, type 2 diabetes mellitus, the insulin resistance syndrome, insulin resistance, impaired glucose tolerance, as well as the stabilisation of blood pressure during haemodialysis.

Particularly preferred conditions include MED and FSD.

Thus, the invention provides a method of treating or preventing a medical condition for which a cGMP PDE5 inhibitor is indicated, in an animal (e.g. a mammal, including a human being), which comprises administering a therapeutically effective amount of the compound of the invention to a mammal in need of such treatment.

Examples

The novel solid form of sildenafil citrate as defined herein may be prepared and characterised according to the Examples and Experimental Methodology sections hereinafter.

PXRD Pattern

Whilst not wishing to be bound by any particular theory it is believed that a key identifier in the PXRD pattern, when generated using the methodology hereinafter, for the hydrated form of sildenafil citrate according to the present invention is the new peak at 5.5°. This peak is not present in the PXRD pattern for the known "anhydrous" form of sildenafil citrate.

Samples of the hydrated sildenafil citrate have been analysed by PXRD using a Bruker D8 Advance X-ray diffractometer using $CuK\alpha_1$ radiation (wavelength =1.5406Å) operating the tube at a voltage of 40KV and a current of 40mA. Samples were prepared by spreading a thin layer of either the dry powder or a slurry of the material of interest on a low background silicon wafer. The samples were irradiated in the X-ray beam which was made parallel using Goebel mirrors with a slit size of 0.2mm and analysed over an angular range of 4-35° two-theta using a Braun position sensitive detector fitted with radial soller slits. Samples were analysed at ambient temperatures (15-30°C) and humidities (40-60%RH).

The PXRD patterns of mixtures of anhydrous sildenafil citrate in buffer(s) that had been slurried at about 4°C for about 72 hours (according to the process detailed above) were compared to the PXRD pattern of anhydrous sildenafil.

Figure 1 illustrates the PXRD patterns for (a) anhydrous sildenafil citrate (non-buffered); (b) sildenafil citrate in phosphate buffer at about pH7.3; (c) sildenafil citrate in citrate buffer at about pH 6.6; and (d) sildenafil citrate in acetate buffer at about pH 4.72.

Figure 1 illustrates that the buffered slurries of the citrate, acetate and phosphate show additional peaks versus the anhydrous form of sildenafil citrate. The peaks at approximately 5.5° and 16.5° two-theta for the buffered solution traces in figure 1 provide evidence of the presence of another solid form.

It is proposed herein that the difference in rate of conversion (to the hydrated form) across the pH range is likely due to the different chemical interactions due to the pKa of the sildenafil molecule.

The solid formed in the phosphate buffered solution of anhydrous sildenafil citrate was isolated and its PXRD pattern is illustrated in Figure 2.

Table 1 illustrates the principal peaks in the PXRD pattern generated at ambient temperatures and RH for the novel hydrated solid form of sildenafil citrate according to the present invention.

Table 1

Angle	Intensity %	Angle	Intensity %	Angle	Intensity %
2-Theta °	%	2-Theta °	%	2-Theta °	%
4.138	66.9	15.132	64.6	25.557	69.9
5.48	98.3	15.71	43.9	26.207	83.7
7.307	66.7	16.537	100	26.798	81.9

8.093	72.3	18.163	46.5	27.698	90.8
10.321	60.5	19.777	55.5	28.964	80.9
10.532	65	20.177	78.9	30.436	82.7
11.068	50.8	20.888	76.5	31.807	73.3
13.123	44.2	22.19	59	34.055	71.4
13.926	86.4	24.018	67.6	34.98	69
14.462	93.3	24.505	67.4	7.554	7.5
14.755	56.2	24.804	60.6	20.607	10.1

Thus the present invention provides a novel form of sildenafil citrate having a PXRD pattern substantially as defined in Table 1 wherein said PXRD pattern is generated using CuKα_1 radiation (wavelength =1.5406Å) when measured according to the method described hereinbefore.

Table 2 provides a further characterisation of the novel solid form of sildenafil citrate wherein the only those peaks having an intensity greater than 80% are illustrated. Again the PXRD pattern illustrated in Table 2 was generated at ambient temperature and relative humidity (as defined hereinbefore for Table 1).

Table 2

Angle	**Intensity %**
2-Theta °	**%**
5.48	98.3

13.926	86.4
14.462	93.3
16.537	100
26.207	83.7
26.798	81.9
27.698	90.8
28.964	80.9
30.436	82.7
26.207	83.7

Thus the present invention provides a novel form of sildenafil citrate having a PXRD pattern substantially as defined in Table 2 wherein said PXRD pattern is generated using $CuK\alpha_1$ radiation (wavelength =1.5406Å) when measured according to the method described hereinbefore.

As will be appreciated by the skilled crystallographer, whilst the relative intensities of the various peaks within Tables 1 and 2 (or in Tables 4, 5, 6 and 7 described hereinafter) may vary due to a number of factors such as for example orientation effects of crystals in the X-ray beam or the purity of the material being analysed or the degree of crystallinity of the sample, the peak positions will remain substantially as defined in Tables 1 and 2. The peak positions shown in Table 1 and 2 (or Tables 4, 5, 6 and 7 discussed hereinafter) may also shift in position depending upon the height of the sample in the X-ray beam as will be appreciated by the skilled crystallographer.

The skilled crystallographer will also appreciate that measurements using a different wavelength will result in different shifts according to the Bragg equation - $n\lambda = 2d \sin \theta$.

Such further PXRD patterns of the novel solid form of sildenafil citrate according to the present invention generated by use of alternative wavelengths are considered to be alternative representations of the PXRD pattern of the crystalline material of the present invention and as such are within the scope of the present invention.

Encompassed within the spirit and scope of the present invention are any polymorphic variants and changes due to variation of the temperature and humidity conditions used during the PXRD analysis of the hydrated and "dehydrated" hydrate forms of sildenafil citrate herein.

NMR Analysis

The novel hydrated form of sildenafil citrate according to the present invention was analysed by ^{1}H NMR.

From the NMR results the stoichiometry of the sildenafil and the citrate portions in the hydrate has been determined to be 1 : 0.75.

Thus the present invention additionally provides a novel solid form of sildenafil citrate wherein the relative amounts of drug to counter ion are present in a molar ratio of 1 : 0.75.

The assignment of the ^{1}H NMR spectrum of the hydrated form of sildenafil citrate (the "tetrahydrate") according to the present invention was based on the known assignment of sildenafil citrate. The analysis was carried out using a Varian INOVA NMR spectrometer, operating at 500 MHz for proton (1H) detection. The acquisition parameters were set up as such to maximise the accuracy of the

integration levels. The ratio of sildenafil : citrate was found to be approximately 1:0.75, by comparison of the integration values for the 2' and 4' protons in the citrate anion with the integration values for the protons in the sildenafil cation. The ^{1}H NMR data is summarised in the listing detailed hereinafter and in Table 3.

Table 3 ^{1}H NMR data for Tetrahydrate of Sildenafil Citrate in DMSO-d6

Atom	δH (ppm)	J (Hz)	Multiplicity	H's
13	0.93	7	triplet	3
21	1.32	7	triplet	3
12	1.74	7	sextet	2
29	2.19	-	singlet	3
25,27	2.43	-	multiplet	4
2',4'	2.59	15	doublet	1.5
2',4'	2.68	15	doublet	1.5
11	2.77	7	triplet	2
24,28	2.93	-	multiplet	4
10	4.14	-	singlet	3
20	4.21	7	quartet	2
18	7.36	9	doublet	1
17	7.81	2,9	doublet of doublets	1
15	7.85	2	doublet	1
5	12.16	-	singlet	1

Peak listing: ^{1}H NMR (500 MHz, DMSO-d6) δ ppm 0.93 (t, *J*=7 Hz, 3 H) 1.32 (t, *J*=7 Hz, 3 H) 1.74 (m, *J*=7 Hz, 2 H) 2.19 (s, 3 H) 2.43 (m, 4 H) 2.59 (d, *J*=15 Hz, 1.5 H) 2.68 (d, *J*=15 Hz, 1.5 H) 2.77 (t, *J*=7 Hz, 2 H) 2.93 (m, 4 H) 4.14 (s, 3 H) 4.21 (q, *J*=7 Hz, 2 H) 7.36 (d, *J*=9 Hz, 1 H) 7.81 (dd, *J*=9, 2 Hz, 1 H) 7.85 (d, *J*=2 Hz, 1 H) 12.16 (s, 1 H)

DSC Analysis

DSC analysis indicated that the compound of the present invention loses water on heating and that the citrate ion degraded on melting of the resultant

"dehydrated" hydrate at 175°C. These observations have been confirmed by EGA analysis as discussed below.

Thermal analysis of a sample of the solid form of the present invention by DSC was performed using a TA Instruments Q1000 DSC heating at 20°C/min with a purge gas of nitrogen and crimped aluminium pans. The results of the DSC analysis are illustrated in Figure 3.

Figure 3 illustrates the heatflow relative to temperature and shows principal events at about 90°C and at about 175°C. The first two events are attributable to a dehydration event and the second event, at about 175°C, is attributable to a melt of the resultant "anhydrous form of the hydrate" with degradation of the citrate ion following the melt (at 195.1°C).

This "anhydrous form" of the solid form of the present invention can be regarded as a "dehydrated" form of the solid form of the present invention and is not to be considered equivalent to anhydrous sildenafil citrate. The melting point of the anhydrous form the "dehydrated hydrate" is 175°C and that of anhydrous sildenafil citrate is 202°C. Further investigations into this "dehydrated hydrate"/anhydrous form are discussed hereinafter.

TGA Analysis

The solid form has been shown by TGA to be present as a tetrahydrate.

A TGA trace showing the relative % weight loss versus temperature for the solid form of the present invention is illustrated in Figure 4. This trace was obtained using a TA Instruments High Resolution 2910 instrument. The sample, ideally about 5 to about 10mg, was heated at 20°C/minute from ambient to 200°C with a purge gas of nitrogen.

Figure 4 illustrates that a weight loss of about 10% was observed when the sample was heated from ambient to about 80°C. Such weight loss, calculated as a potential water loss from anhydrous sildenafil citrate (1 : 0.75) salt indicates that the new solid form is present as a tetra (4) hydrate salt.

The solid form remaining after the first weight loss is regarded as the "dehydrated hydrate" / anhydrous form identified via DSC and illustrated in Figure 3. Further heating of this "dehydrated hydrate" form results in a second weight loss of about 18%, observed at temperatures in excess of 150°C.

EGA Analysis

To further investigate the processes occurring during the heating ramp Evolved Gas Analysis (EGA) was performed on the sildenafil citrate solid form of the present invention. This technique monitors the weight lost during heating whilst simultaneously quantifying the components of the evolved gas using mass spectrometry (MS). This provides data relating to any desolvation/degradation processes.

To determine the composition of the matter lost on heating, the exhaust gas from TGA apparatus was fed into a quadropole mass spectrometer. This TGA trace (illustrated in Figure 5) was obtained using a TA Instruments Q50 TGA with platinum pans. The sample, ideally from about 5mg to about 10mg, was heated at 20°C/minute from ambient to 200°C with a purge gas of helium. The exhaust gas was analysed by a Pfeifer Thermostar Mass spectrometer working in "trend" mode. Ions 17 and 18 corresponding to water and 44 for carbon dioxide were monitored. Ion currents, which are traces displaying the weight loss versus temperature, for each of the specific ions are also illustrated in Figure 5.

Figure 5 shows a trace of the TGA (see Figure 3) combined with the signals for mass ions 17 & 18 (water) and 44 (carbon dioxide).

In line with the initial TGA analysis (illustrated in Figure 4 as discussed hereinbefore) Figure 5 also illustrates that a % weight loss of about 10% is observed during the initial heating stage (at from about RT to about 80°C).

The traces related to the relative increase in the release of mass ions 17 and 18 indicate that release of water have been detected (by MS) during this lower temperature initial loss period. Based on these results this first weight loss can be attributed to release of the bound water from within the crystal lattice.

Analysis of the relative release of mass ions 17, 18 and 44 during the second period of weight loss, at higher temperatures (corresponding to about 18%) at from about 150°C to about 200°C indicates that both water and carbon dioxide are emitted. This is consistent with weight loss attributable to the degradation of the citric acid in the sample of the "dehydrated" form of the sildenafil citrate tetrahydrate.

According to a further aspect the present invention provides a novel anhydrous form of sildenafil citrate (I) and a process for its preparation. Such novel anhydrous form has been described hereinbefore as a "dehydrated" hydrate of sildenafil citrate tetrahydrate. Dehydrated hydrates are discussed in Stephenson, G. A., Groleau, E.G., Kleiman, R. L., Xu, W., Rigsbee, D. R., J. Pharm. Sci. 87(5) (1998), pages 536 – 542 incorporated herein by reference.

The presence of said dehydrated hydrate has been discussed in relation to DSC, TGA and EGA analyses. The structure of the dehydrated hydrate has been identified using simultaneous scanning for structure via hot stage PXRD and low humidity PXRD of sildenafil citrate tetrahydrate.

Hot stage powder X-ray diffraction was been performed using a Bruker D8 X-ray powder diffractometer fitted with Goebel mirrors and a Braun position sensitive

detector. The sample of sildenafil citrate tetrahydrate was radiated using CuKα radiation. The sample of sildenafil citrate tetrahydrate was presented on a silicon wafer and heated to 100°C at a rate of 0.1°C/sec using the Anton Paar heating stage fitted to the system. Following analysis at 100°C the sample was allowed to cool to ambient and reanalysed five minutes and 2 hours after reaching ambient.

Low humidity PXRD was performed using an Ansyco humidity line model Sycos-H (AXS) using nitrogen as a carrier gas.

Figure 6 illustrates the relative changes in the PXRD pattern associated with a sample of sildenafil citrate tetrahydrate when subjected to different heat treatments: RT; 100°C (for about 20 minutes); 5 minutes after removal of 100°C heat (i.e. 5 minutes cooling); and 2 hours after removal of 100°C heat.

As illustrated in Figure 6, hot stage analysis reveals that the characteristic peaks attributable to the tetrahydrate are not present in the PXRD pattern for the sample analysed at 100°C. The peaks illustrated at 100°C are attributable to a new "dehydrated hydrate". The peak positions of this "dehydrated" hydrate may be shifted due to the thermal expansion of the atoms in the crystal lattice as will be appreciated by the skilled crystallographer. Figure 6 further demonstrates that on cooling, after 2 hours the tetrahydrate form is reproduced. These results indicate that on reaching 100°C a new hygroscopic form has been produced which potentially due to its hygroscopicity reconverts to the hydrated form on returning to ambient temperatures.

Table 4 provides the peak positions of the dehydrated hydrate.

Table 4 Peak positions for dehydrated hydrate

Angle	Intensity %	Angle	Intensity %	Angle	Intensity %
2-Theta °		2-Theta °		2-Theta °	
5.936	2.2	16.306	9.1	23.887	2.3
6.522	55.9	17.101	2	24.223	8.1
7.658	100	17.83	32.2	24.546	2.1
8.141	30.9	18.242	3.4	24.985	2.1
8.916	2.2	19.163	4.9	25.592	2.6
10.395	15.9	19.494	2.3	26.106	3.4
11.751	4.5	20.019	7.7	26.645	8.5
12.092	17.4	20.498	5.6	27.006	3.5
13.009	15.6	20.861	11.5	27.67	1.7
13.643	31.4	21.51	2.6	29.048	3.7
14.078	3.9	21.761	3	29.942	3.2
14.509	24.8	22.097	2.3	30.71	2
14.915	8.9	22.816	3.9	31.305	2.5
15.303	9.3	23.172	2.5	32.314	1.4
16.032	5.2	23.524	2.4	32.899	1.8
				34.362	3

Thus the present invention provides a further novel form of sildenafil citrate having a PXRD pattern substantially as defined in Table 4 wherein said PXRD pattern is generated using $CuK\alpha_1$ radiation (wavelength =1.5406Å) and at 0% relative humidity when measured according to the method described hereinbefore.

Table 5 Peak positions for dehydrated hydrate having at least 10% Intensity

Angle	Intensity %
2-Theta °	
6.522	55.9
7.658	100
8.141	30.9

10.395	15.9
12.092	17.4
13.009	15.6
13.643	31.4
14.509	24.8
17.83	32.2
20.861	11.5

Thus the present invention provides a further novel form of sildenafil citrate having a PXRD pattern substantially as defined in Table 5 wherein said PXRD pattern is generated using $CuK\alpha_1$ radiation (wavelength =1.5406Å) and at 0% relative humidity when measured according to the method described hereinbefore.

The traces in Figure 7 indicate that on reduction of humidity (lower RH values) intermediate hydrated forms are present. At high humidity (90%RH) the trace is comparable to that of the sildenafil citrate tetrahydrate illustrated in Figure 2. On reducing the relative humidity (from 90%) in 10% steps no changes are observed until the humidity reaches 40% where the trace converts to a different hydrated form. Further stepwise reductions in humidity produce slight changes in the patterns with the major peak at an angle of 5.5° 2θ moving to higher angles. Without being bound to any particular theory we propose that this suggests a "contraction" is occurring within the crystal as water moves out of the lattice.

Thus the present invention additionally provides further hydrated forms of sildenafil citrate (1 : 0.75) at 40% RH, 20% RH and 10% RH having principal PXRD peaks as illustrated in Figure 7.

Figure 8 illustrates the PXRD pattern of the hydrated form of sildenafil citrate observed at 40% RH.

According to a further embodiment the present invention provides a solid form having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined in Table 6 wherein said PXRD pattern is generated using CuKα_1 radiation at a wavelength of 1.5406Å and at ambient temperature and 40% RH.

Table 6

Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %
5.979	66	18.232	2.8	26.946	2.8
7.314	11.5	18.622	1.5	27.379	7.7
7.961	100	19.53	3.4	28.648	1.6
10.384	15.6	19.94	6.4	28.995	3.2
10.632	3.9	20.171	4	29.324	3
10.964	1.6	20.768	6	29.949	2.9
12.012	11.6	21.202	3	30.535	1.8
13.26	3.4	21.596	3.6	31.223	1.7
13.98	32.8	22.759	5.6	31.662	1.7
14.476	40.8	23.466	2.1	32.014	2.1
14.873	4.6	23.867	3.3	32.624	1.3
15.342	2	24.148	11.8	32.768	1.3
15.949	2	24.896	2.2	33.435	1.3
16.269	5.3	25.097	2.1	33.766	2
16.505	2.9	25.672	1.5	34.083	1.7
17.268	37.4	26.098	3.1	34.859	1.4
17.868	8	26.551	2.5		

Table 7 illustrates the principal peaks of the solid form observed at 40%RH (i.e. those having an intensity of > 10%). Thus according to a further still aspect the present invention provides a solid form having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined in Table 7 and wherein said PXRD pattern is generated using CuKα_1 radiation (wavelength =1.5406Å) at ambient temperature and 40% relative humidity.

Table 7

Angle 2-Theta °	Intensity %
5.979	66
7.314	11.5
7.961	100
10.384	15.6
12.012	11.6
13.98	32.8
14.476	40.8
17.268	37.4
24.148	11.8

It has been demonstrated that the hydrated solid form according to the present invention is a stable and robust material. Once produced it is not been possible to regenerate anhydrous sildenafil citrate from this hydrated solid form either by drying at temperatures from ambient to 100°C or at low humidities (e.g. 0% RH). Hydrates are conventionally difficult to dry. Whilst under certain conditions the hydrated solid form can be converted into a "dehydrated" form it has been demonstrated that this "dehydrated" form returns to the hydrated solid form on cooling.

PREPARATIONS

Preparation 1 - 5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one monocitrate

A solution of 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one in a suitable organic solvent was heated up to the reflux temperature of the solvent whereupon an aqueous solution of citric acid was added. The product was isolated from the solution via filtration as a white crystalline solid, m.p. around 195°C. Found: C,50.51; H,5.60; N,12.59. $C_{22}H_{30}N_6O_4S$; $C_6H_8O_7$ requires C,50.44; H,5.75; N,12.61 %.

Preparation 2 – Formation of sildenafil citrate tetrahydrate from sildenafil monocitrate (anhydrous sildenafil citrate)

Anhydrous sildenafil citrate (250mg) in 2ml of 0.2M phosphoric acid buffer (prepared according to the procedure hereinafter) was slurried (using a rotating bed) at about 4°C for about 72 hours. The resultant solid was isolated using vacuum filtration and allowed to dry at ambient temperature and humidity. The sample was analysed by PXRD, ^{1}H. Nmr, TGA and EGA as detailed hereinbefore and characterised as the tetrahydrate of sildenafil citrate (1 : 0.75).

Preparation of pH 4.76 Acetic Acid Buffer [0.2 molar]

12.01 grams of Glacial Acetic Acid was weighed into a 1 litre beaker and approximately 400 mls of water was carefully added. The pH was adjusted to 4.76 with concentrated NaOH [carbonate free] - 'CONVOL' concentrate is suitable. The solution was transferred quantitatively to a 1 litre volumetric flask and made up to 1 litre. The buffer solution was divided, in 25ml aliquots, to 50ml vials and sealed prior to autoclaving the vials and storing at 4°C.

'ANALAR' grade, or similar, chemicals and milliq de-ioised water were used in the preparation of this buffer. When using the buffer it can, if necessary, be diluted to 1:20 to give an in-use concentration of 0.01M and NaCl [0.67% $^{w}/_{v}$] can be added to maintain chloride ion concentration and ionic strength.

Preparation of pH 6.4 Citric Acid Buffer [0.2 molar]

This buffer can be prepared according to the general procedure detailed in Preparation 1. Weigh 38.42 grams of Anhydrous Citric Acid into a 1 litre beaker and add approximately 150 mls of water (maximum). 42.02 grams of Citric Acid Monohydrate can alternatively be used. Adjust the pH to 6.4 with concentrated

NaOH [carbonate free] - 'CONVOL' concentrate is suitable. The solution can be transferred into vials as detailed herein before.

Preparation of pH 7.20 Phosphoric Acid Buffer [0.2 molar]

This buffer can be prepared according to the general procedure detailed in Preparation 1. Weigh 19.60 grams of concentrated orthophosphoric acid into a 1 litre beaker and carefully add approximately 200 mls of water (maximum). Adjust the pH to 7.20 with concentrated NaOH [carbonate free] - 'CONVOL' concentrate is suitable. The solution can be transferred into vials as detailed herein before.

CLAIMS

1. A solid form of sildenafil citrate wherein the ratio of sildenafil : citrate is 1 : 0.75.

2. Sildenafil citrate tetrahydrate.

3. Sildenafil citrate tetrahydrate wherein the ratio of sildenafil : citrate is 1 : 0.75.

4. A solid form of sildenafil citrate having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined below:

Angle 2-Theta °	Intensity % %	Angle 2-Theta °	Intensity % %	Angle 2-Theta °	Intensity % %
4.138	66.9	15.132	64.6	25.557	69.9
5.48	98.3	15.71	43.9	26.207	83.7
7.307	66.7	16.537	100	26.798	81.9
8.093	72.3	18.163	46.5	27.698	90.8
10.321	60.5	19.777	55.5	28.964	80.9
10.532	65	20.177	78.9	30.436	82.7
11.068	50.8	20.888	76.5	31.807	73.3
13.123	44.2	22.19	59	34.055	71.4
13.926	86.4	24.018	67.6	34.98	69
14.462	93.3	24.505	67.4	7.554	7.5

14.755	56.2	24.804	60.6	20.607	10.1

wherein said PXRD pattern is generated using CuKα_1 radiation at a wavelength of 1.5406Å and at ambient temperature and humidity.

5. A solid form of sildenafil citrate according to any of claims 1 to 3 wherein the solid form has a PXRD pattern as defined in claim 4.

6. A solid form of sildenafil citrate having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined below:

Angle	**Intensity %**
2-Theta °	**%**
5.48	98.3
13.926	86.4
14.462	93.3
16.537	100
26.207	83.7
26.798	81.9
27.698	90.8
28.964	80.9
30.436	82.7
26.207	83.7

wherein said PXRD pattern is generated using $CuK\alpha_1$ radiation at a wavelength of 1.5406Å and at ambient temperature and humidity.

7. A process for the preparation of a solid form of sildenafil citrate according to any of claims 1 to 6 from anhydrous sildenafil citrate wherein said process comprises treating anhydrous sildenafil citrate with aqueous acid/base buffers in the range of from about pH 4 to about pH 7.5.

8. A process according to claim 7 wherein the buffer solution is at from about pH 6.3 to about pH 7.3, preferably at from about pH 6.4 to about pH 7.2.

9. A process for the preparation of sildenafil citrate tetrahydrate according to either of claims 7 or 8 wherein the buffered solution is treated at about 4°C.

10. The product obtainable by the process of any of claims 7 to 9.

11. A solid form of sildenafil citrate having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined below:

Angle	Intensity %	Angle	Intensity %	Angle	Intensity %
2-Theta °		2-Theta °		2-Theta °	
5.936	2.2	16.306	9.1	23.887	2.3
6.522	55.9	17.101	2	24.223	8.1
7.658	100	17.83	32.2	24.546	2.1
8.141	30.9	18.242	3.4	24.985	2.1
8.916	2.2	19.163	4.9	25.592	2.6
10.395	15.9	19.494	2.3	26.106	3.4
11.751	4.5	20.019	7.7	26.645	8.5
12.092	17.4	20.498	5.6	27.006	3.5
13.009	15.6	20.861	11.5	27.67	1.7
13.643	31.4	21.51	2.6	29.048	3.7

14.078	3.9	21.761	3	29.942	3.2
14.509	24.8	22.097	2.3	30.71	2
14.915	8.9	22.816	3.9	31.305	2.5
15.303	9.3	23.172	2.5	32.314	1.4
16.032	5.2	23.524	2.4	32.899	1.8
				34.362	3

wherein said PXRD pattern is generated using CuKα_1 radiation at a wavelength of 1.5406Å and at ambient temperature and 0% RH.

12. A solid form of sildenafil citrate having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined below:

Angle 2-Theta °	Intensity %
6.522	55.9
7.658	100
8.141	30.9
10.395	15.9
12.092	17.4
13.009	15.6
13.643	31.4
14.509	24.8
17.83	32.2
20.861	11.5

wherein said PXRD pattern is generated using CuKα_1 radiation (wavelength =1.5406Å) at ambient temperature and 0% relative humidity.

13. A solid form of sildenafil citrate having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined below:

Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %	Angle 2-Theta °	Intensity %
5.979	66	18.232	2.8	26.946	2.8
7.314	11.5	18.622	1.5	27.379	7.7
7.961	100	19.53	3.4	28.648	1.6
10.384	15.6	19.94	6.4	28.995	3.2
10.632	3.9	20.171	4	29.324	3
10.964	1.6	20.768	6	29.949	2.9
12.012	11.6	21.202	3	30.535	1.8
13.26	3.4	21.596	3.6	31.223	1.7
13.98	32.8	22.759	5.6	31.662	1.7
14.476	40.8	23.466	2.1	32.014	2.1
14.873	4.6	23.867	3.3	32.624	1.3
15.342	2	24.148	11.8	32.768	1.3
15.949	2	24.896	2.2	33.435	1.3
16.269	5.3	25.097	2.1	33.766	2
16.505	2.9	25.672	1.5	34.083	1.7
17.268	37.4	26.098	3.1	34.859	1.4
17.868	8	26.551	2.5		

wherein said PXRD pattern is generated using $CuK\alpha_1$ radiation at a wavelength of 1.5406Å and at ambient temperature and 40% RH.

14. A solid form of sildenafil citrate having a powder X-ray diffraction (PXRD) pattern with main peaks substantially as defined below:

Angle 2-Theta °	Intensity %
5.979	66
7.314	11.5
7.961	100
10.384	15.6
12.012	11.6
13.98	32.8
14.476	40.8
17.268	37.4
24.148	11.8

wherein said PXRD pattern is generated using $CuK\alpha_1$ radiation (wavelength =1.5406Å) at ambient temperature and 40% relative humidity.

ABSTRACT

A novel solid form of sildenafil citrate wherein the ratio of sildenafil : citrate is 1 : 0.75.

Figure 1

PXRD traces of slurries of Sildenafil citrate at different pH's

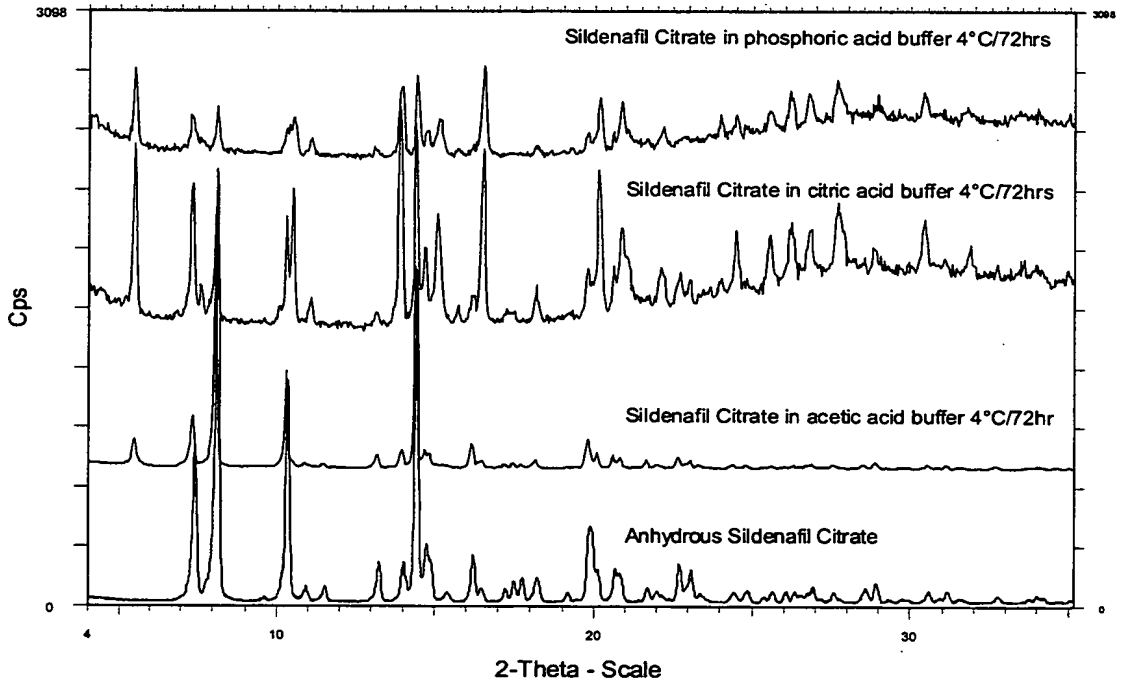


Figure 2

PXRD analysis of new form of sildenafil citrate (in phosphate buffer) versus anhydrous sildenafil citrate

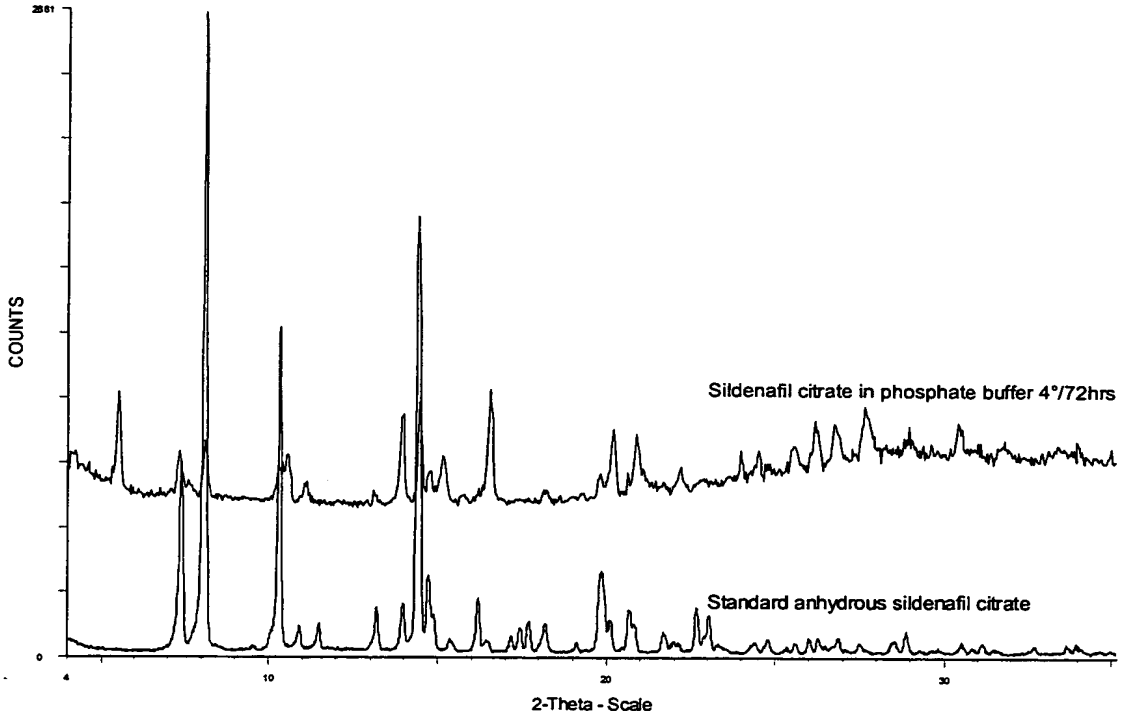


Figure 3

DSC Trace of Sildenafil citrate tetrahydrate

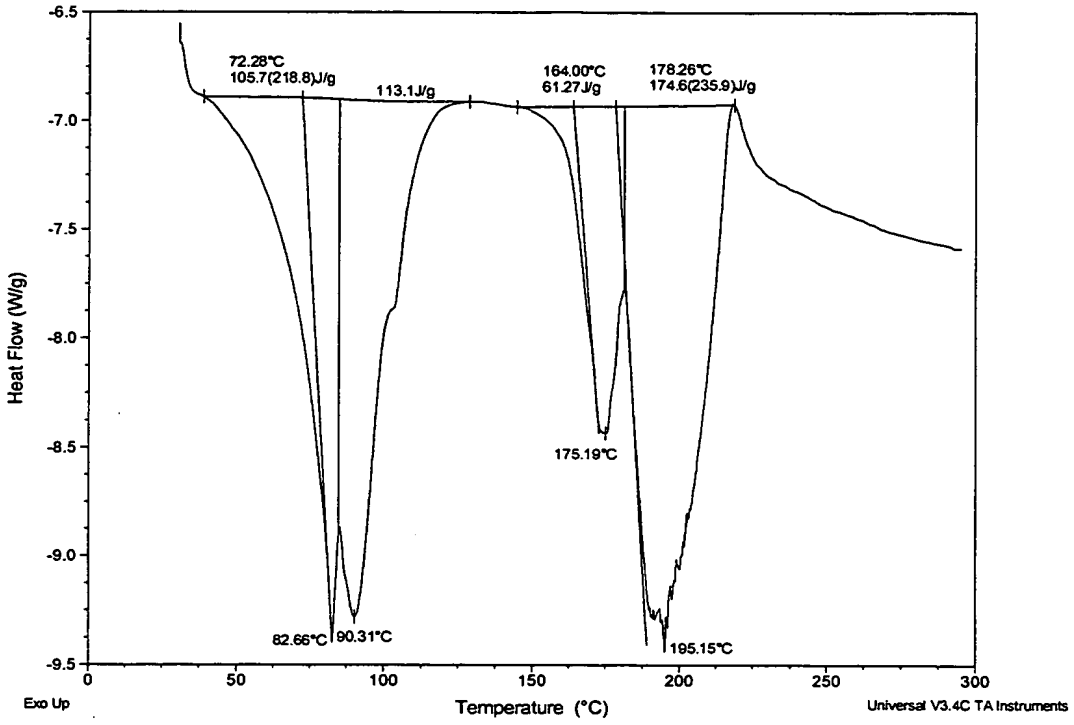


Figure 4

TGA Analysis of Solid Form of Sildenafil Citrate

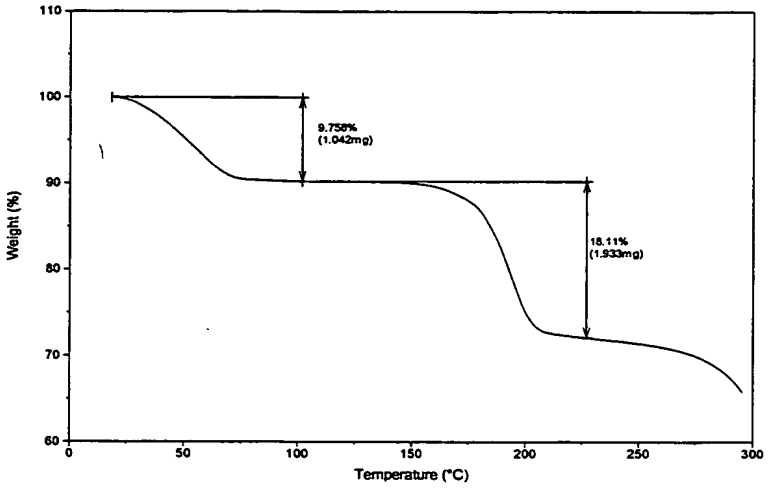


Figure 5

EGA trace for Sildenafil Citrate Tetrahydrate showing the detection of water (mass ions 17 and 18) and Carbon dioxide (mass ion 44)

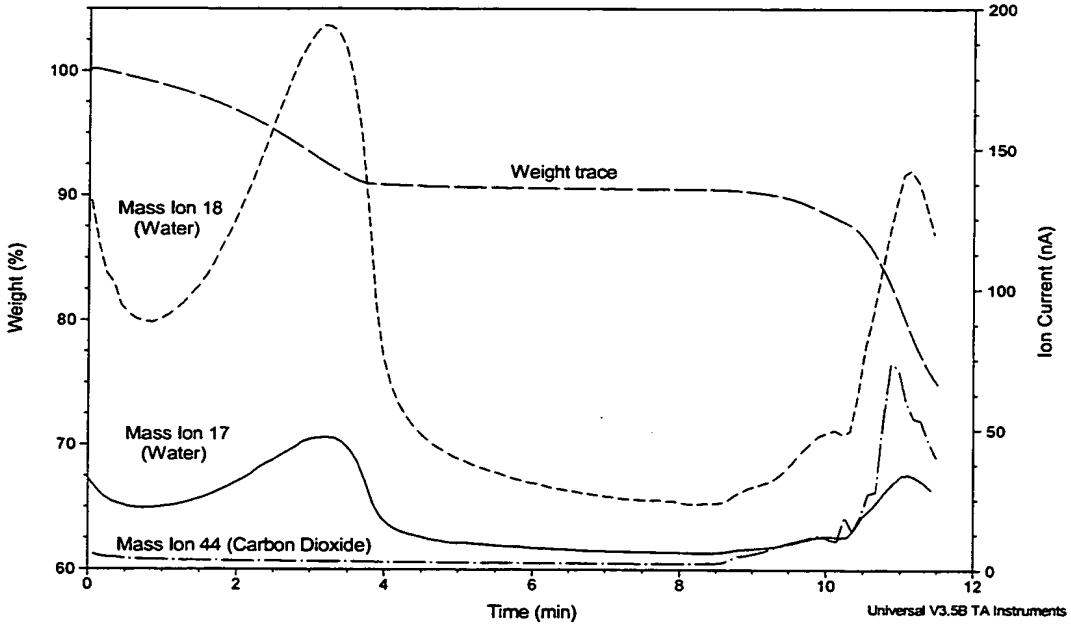


Figure 6

Hot stage PXRD analysis of sildenafil citrate tetrahydrate solid form

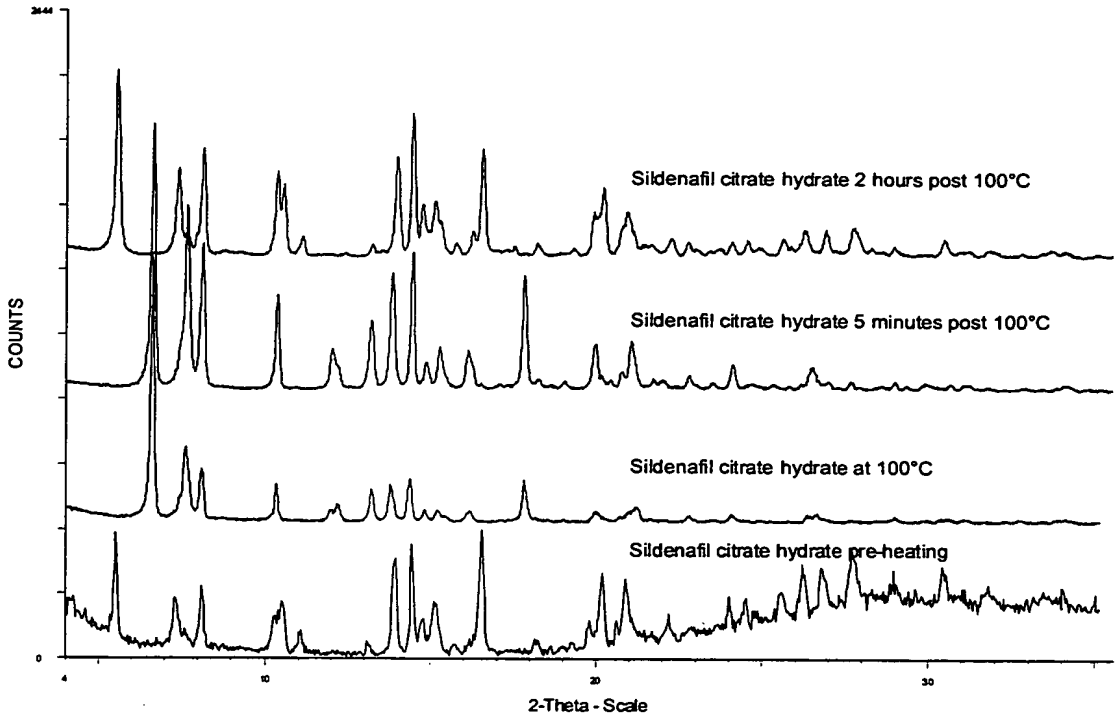


Figure 7

PXRD analysis of Sildenafil citrate tetrahydrate at different humidities

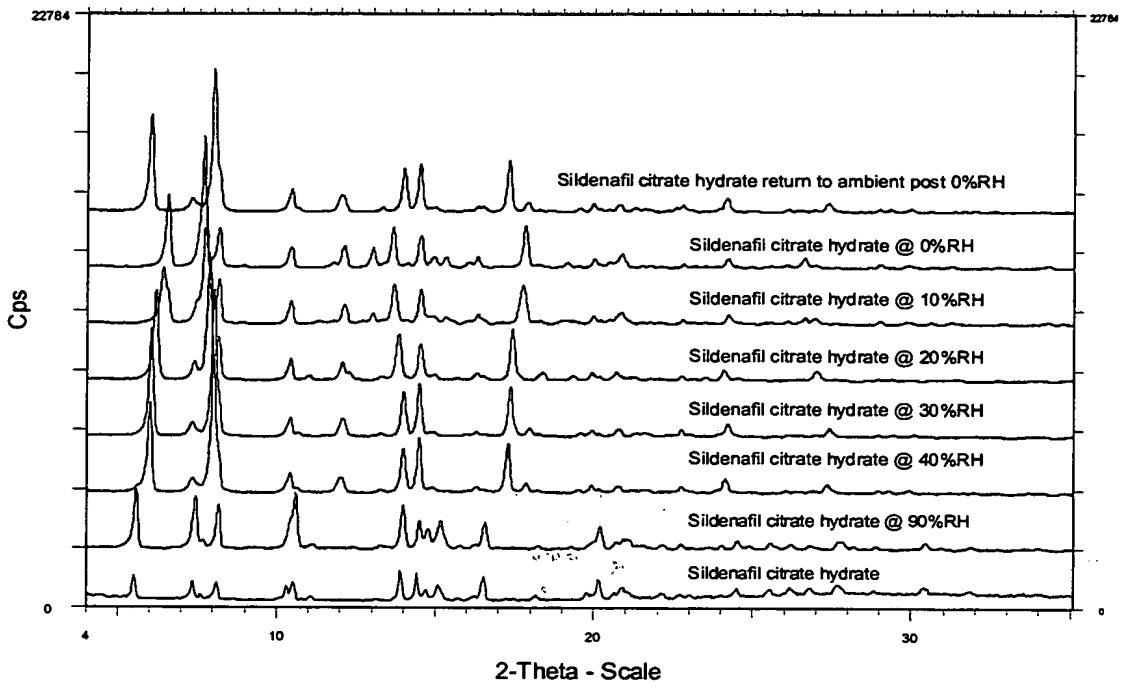


Figure 8

PXRD analysis of further hydrated form of Sildenafil Citrate observed at 40% RH